UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Office of Prevention, Pesticides and Toxic Substances

July 6, 2000

MEMORANDUM

SUBJECT: ***Dichlorvos*****:** Response to the Registrant's (AMVAC Chemical Company) Supplemental Comments on the Draft Preliminary Risk Assessment

DP Barcode: D267223 PC code: 084001
Submission No.: S581910

TO: Robert McNally
Reregistration and Special Review Division (7508W)

FROM: Sanjivani Diwan
Senior Toxicologist
Reregistration Branch 4/HED (7509C)

THROUGH: Susan Hummel
Branch Senior Scientist
Reregistration Branch 4/HED (7509C)

On June 30, 2000, AMVAC submitted additional comments to supplement the previous correspondence regarding significant errors in the draft preliminary risk assessment (PRA) for dichlorvos (DDVP) dated April 15, 2000. The registrant disagrees with OPP's position on the selection of toxicology endpoint for "short-term inhalation and dermal" exposure scenario because decreased body weight and cholinergic signs at 2.5 mg/kg/day did not occur in the study. Therefore, the Agency cannot base its exposure scenarios on them.

Registrant's comment: AMVAC stated that the errors in PRA are made with respect to answers to two issues: 1. What exposure scenarios for DDVP uses are appropriately described as "short-term"?;

2. What toxicology study and endpoint should be used for risk assessment purposes for "short-term" exposures to DDVP?

AMVAC reported that 1) neither an effect on body weight nor a treatment-related effect on clinical observations occurred in the study in the 2.5 mg/kg/day exposure group during treatment with DDVP; and 2) treatment-related clinical signs were seen only at 7 mg/kg/day and not at 2.5 mg/kg/day. The body weight was not statistically affected by treatment at any dosage level. Therefore, the NOAEL for maternal toxicity for 1-7 days exposure should be 2.5 mg/kg/day and the LOAEL should be 7 mg/kg/day based on clinical signs. AMVAC further stated that residential spraying of a pressurized aerosol spray can would not occur repeatedly for seven continuous days.

Agency's response: The endpoint selected for short-term residential dermal/inhalation exposure risk assessment was based on a rabbit developmental study (Tyl et al., 1991a; MRID 41802401). The dose selected was a maternal NOAEL of 0.1 mg/kg/day based on decreases in body weight gain at 2.5 mg/kg/day. Hazard Identification Assessment Review Committee (HIARC) made a selection of endpoint based on the Agency's (HED) independent evaluation of the data in the study report and not what was reported in the study report. HED has evaluated this study and the Data Evaluation Report (DER) indicated that the treatment-related decrease in maternal body weight gain during gestation days (GDs) 7-19 (approx. 12 days) was noted at 2.5 and 7 mg/kg/day. The dose-related decrease in body weight gain (32.6% and 42.0% at 2.5 and 7 mg/kg/day, respectively), although not statistically significant, was considered to be biologically significant. A dose-related increase in maternal mortality was also noted at 2.5 and 7 mg/kg/day. In fact the study authors' conclusion is consistent with HED's evaluation that the maternal toxicity was observed at 2.5 and 7 mg/kg/day and the NOAEL for maternal toxicity was 0.1 mg/kg/day. The Agency agrees with the Registrant that treatment-related cholinergic signs were observed only at the next higher dose level, 7 mg/kg/day (see attachment; page # 5 of the DER). However, HIARC document inadevertantly reported that the basis for the NOAEL of 0.1 mg/kg/day for maternal toxicity was based on the cholinergic signs and decreases in body weight at 2.5 mg/kg/day. Consequently, the endpoint is decrease in body weight gain and not decreases in body weight and clinical signs. Although the term "Short-term" is not defined in the PRA, the "Short-term" exposure duration is for a period of 1 to 7 days as described in the Toxicology Endpoint Selection Guidance document (April 11, 1998). The Agency acknowledges the fact that residential spraying of a pressurized aerosol spray can would not occur repeatedly for seven continuous days. Nevertheless, there is a concern for continual exposure to DDVP for several days following the spraying.

Registrant's comment: AMVAC further stated that the toxicological endpoint selected by EPA from the rabbit developmental study is not acceptable for risk assessment because 1) rabbits are variable from lot to lot and are not consistent with respect to subchronic toxicity endpoints; 2) rabbits are prone to respiratory infections that result in sporadic deaths.....; 3) the rabbit developmental study does not demonstrate effect of DDVP on body weight or clinical observations in the 2.5 mg/kg/day group from 1-7 days of treatment; and the NOAEL of 0.1 mg/kg/day selected by the EPA is not in agreement with other short-term studies in either rats or rabbits. In fact the NOAEL of 2.5

mg/kg/day for maternal toxicity for 1-7 days of exposure is consistent with other developmental studies in rabbits and rats.

Agency's response: In the absence of a dermal toxicity study, the HIARC routinely selects an oral study for dermal or inhalation exposure risk assessment and this approach was accepted by the Scientific Advisory Panel. According to the Agency's FIFRA Subdivision F Guidelines, rabbit is one of the species selected for assessing developmental toxicity. The dose-related maternal deaths that occurred in the developmental study were clearly treatment-related and were not caused by respiratory infection. It should be noted that no deaths occurred in control animals. The Agency agrees that the clinical signs were seen only at 7 mg/kg/day (refer to Page# 5 of the DER), however, the decrease in body weight gain occurred during GDs 7-19 at both 2.5 and 7 mg/kg/day. Therefore, the Agency supports it earlier position regarding the NOAEL and LOAEL (for maternal toxicity) of 0.1 and 2.5 mg/kg/day, respectively, as well as the toxicological endpoint selected for risk assessment. The NOAEL of 0.1 mg/kg/day is in fact the lowest NOAEL reported among the developmental studies available (Schwetz et al., 1979 and Tyl et al., 1991b).

References cited

Schwetz, B.A., Isoet, H.D., Leong, B.K.J., and Staples, R.E. (1979). Teratogenic potential of dichlorvos given by inhalation and gavage to mice and rabbits. Teratology 20:383-387.

Tyl, R., Marr, M., and Myers, C. (1991a). Developmental toxicity evaluation of DDVP administered by gavage to New Zealand rabbits. Lab Project Number: 60C-4629-30/40. Unpublished study prepared by Research Triangle Institute. MRID 41802401

Tyl, R., Marr, M., and Myers, C. (1991b). Developmental toxicity evaluation of DDVP administered by gavage to CD (Sprague-Dawley) rats. Lab Project Number: 60C-4629-10/20. Unpublished study prepared by Research Triangle Institute. MRID 41951501

Attachment

cc: Ray Kent/Branch Chief, RRB4

ICHA_VJ

FINAL
DOC 930190

009840

DATA EVALUATION REPORT

DICHLORVOS

Study Type: Developmental Toxicity Study in Rabbits

Prepared for:

Healths Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer Sanju Diwan Date 10/9/92
Sanju Diwan, Ph.D.

Independent Reviewer Pia Lindström Date 10/9/92
Pia Lindström, D.V.M.

QA/QC Manager Sharon Segal Date 10/13/92
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 1-128
Clement Number: 93-126
Project Officer: James Scott

EPA Reviewer
and Section Head: Joycelyn Stewart, Ph.D.
Toxicology Branch I/HED

Signature: Joycelyn Stewart
Date: 11/4/92
HSR 11/5/92

DATA EVALUATION REPORT

STUDY TYPE: Developmental toxicity study in rabbits

EPA IDENTIFICATION NUMBERS

Tox Chem. No.: EPA Registration No. 5481-96

MRID No.: 418024-01

TEST MATERIAL: Dimethyl 2,2-dichlorovinyl phosphate

SYNONYMS: Dichlorvos, DDVP, UDVF, Cekusan, Cypona, Devikol, Duo-Kill, Duravos, Herkol, Marvex, No-Pest, Prentox, Verdican, Verdipor, Verdisol, Ciovap, Ravap, Elastrel

SPONSOR: AMVAC Chemical Corporation, Los Angeles, CA

STUDY NUMBER: 60C-4629-30/40

TESTING FACILITY: Research Triangle Institute, Research Triangle Park, NC

TITLE OF REPORT: Developmental Toxicity Evaluation of DDVP Administered by Gavage to New Zealand White Rabbits

AUTHORS: Tyl, R.W., Marr, M.C., Myers, C.B.

REPORT ISSUED: February 22, 1991

CONCLUSIONS: A developmental toxicity study was conducted in which New Zealand White Rabbits were administered dichlorvos via gavage at 0, 0.1, 2.5, or 7.0 mg/kg/day during gestational days (GDs) 7-19, inclusive. Maternal toxicity, observed at 2.5 and/or 7.0 mg/kg/day, was manifested as an increased incidence of mortality, clinical signs (cholinergic), and decreased body weight, and body weight gain during the dosing period. Based on these results, the maternal NOEL and LOEL were 0.1 and 2.5 mg/kg/day, respectively.

Developmental toxicity was not observed in this study. Consequently, the NOEL for developmental toxicity was >7.0 mg/kg/day; the LOEL was not determined.

CLASSIFICATION: Core Minimum Data.

A. MATERIALS

Test Compound

Purity: 97%
Stability: Stable under normal use and storage conditions
Specific gravity: 1.424 g/mL
Density: ≥1
Description: Colorless to amber liquid
Lot number: 802097
Receipt date: December 29, 1989
Contaminants: Not reported

Vehicle: Deionized/distilled water

Test Animals

Species: Rabbit
Strain: New Zealand White rabbit
Source: Hazleton Research Products, Inc., Denver, PA
Age: 6 months on GD 0
Weight: 2520-3670 g on GD 0
Males used: Same strain from the RTI breeding colony originally from the same supplier

B. STUDY DESIGN

This study was designed to assess the potential of dichlorvos to cause developmental toxicity in rabbits when administered daily via gavage from GD 7 through 19, inclusive.

Mating: Following 14 days of acclimation, females were artificially inseminated. Ovulation was induced by an intravenous injection of Pregnyl (chorionic gonadotropin). Semen was collected from the RTI male breeding colony using an artificial vagina (Bredderman et al. 1964) in conjunction with a teaser female. Females were inseminated with approximately 0.25 mL of undiluted ejaculate.

Animal husbandry: Food (#5322 Purina Certified Rabbit Chow) and deionized/filtered tap water were available ad libitum throughout the study. A 12/12-hour light/dark cycle was maintained. Temperature and relative humidity ranges were 63.6°-70.4°F and 48.3%-88.3%, respectively.

Group arrangement: Animals were allocated to the following dose groups using a stratified randomization method based on GD 0 body weight.

Test Group	Dose Level (mg/kg/day)	Number Assigned per Group
Control	0	16
Low dose	0.1	16
Mid dose	2.5	16
High dose	7.0	16

Dose administered: Doses were administered daily via gavage from GD 7 through 19 in a volume of 1.0 mL/kg. The most recently recorded body weights were used to calculate the concentration of the doses. The report did not state whether the dosing solutions were adjusted for active ingredient. Doses were prepared three times during the study and refrigerated. Prior to study initiation, dose levels were verified and homogeneity and stability were determined. Triplicate samples of the dosing solutions were analyzed by high-performance liquid chromatography.

Dose rationale: The doses were selected based on the results of a range-finding study (no. 60C-4629-30) conducted in the same strain of 47 pregnant rabbits at dose levels of 0, 0.1, 1.0, 2.5, 5.0, or 10 mg/kg/day (8 per group, except for 7 in the 2.5-mg/kg/day group). Maternal toxicity, evident at 10 mg/kg/day, was manifested as increased mortality (5/8 does treated at high dose died during the study), clinical signs, and decreased body weight gain. Maternal cholinesterase activity was significantly reduced in a dose-related manner at 1.0, 2.5, 5.0, and 10 mg/kg/day. The percentages of plasma cholinesterase activity inhibition were 74.1%, 60.9%, 32.8%, and 18.6%, respectively. The percentages for RBC cholinesterase activity inhibition were 64.5%, 43.4%, 19.0%, and 14.5%, respectively. Developmental toxicity, evident at 10 mg/kg/day, was manifested as a slight but nonsignificant decrease in fetal body weight.

Observations: Animals were observed daily for mortality, moribundity, and overt signs of toxicity in addition to observations conducted twice a day and 1-2 hours postdosing during the dosing period. Body weight was recorded on GDs 0, 7, 9, 12, 15, 19, 23, and 30. Food consumption was recorded for the following periods: GDs 0-7, 7-9, 9-12, 12-15, 15-19, 19-23, and 23-30. On GD 30, does were sacrificed by intravenous injection of Beuthanasia, and litters were delivered by cesarean section. Examination of the does at sacrifice included the following:

- Gross pathology observations of the organs and abdominal and thoracic cavities were conducted.
- Body weights were recorded.
- Gravid uterine weights were recorded.

- Liver weights were recorded and the livers were stored in fixative for possible future evaluation.

- Number of corpora lutea, implantation sites, resorptions and live and dead fetuses were recorded.

Uteri from apparently nonpregnant animals were stained with 10% ammonium sulfide to detect early embryo loss.

Live fetuses were examined in the following manner:

- Individual fetuses were weighed.

- External anomalies (including cleft palate) were recorded for all fetuses.

- Visceral anomalies and confirmation of sex were recorded for all fetuses using a fresh tissue dissection method (Staples 1974; Stuckhardt and Poppe 1984). Approximately half of the fetal heads were fixed in Bouin's solution and then evaluated using the free-hand sectioning technique by Wilson (1965).

- Skeletal anomalies were recorded for all fetuses following evisceration, maceration, and staining with Alcian Blue/Alizarin Red S (Marr et al. 1988).

Statistical analysis: The following methods were used.

- Maternal body weight and body weight gain, fetal body weight, food consumption, gravid uterus and liver weights, and numbers of corpora lutea, implantation sites, and live fetuses per litter--Bartlett's test for homogeneity, ANOVA, linear trend test, and Dunnett's test for pairwise comparisons;

- Percent preimplantation loss, resorptions, dead fetuses, nonalive and affected implants, males, fetuses with anomalies per litter--Arcsine square root transformation, Bartlett's test for homogeneity, linear trend test, and ANOVA; and

- Numbers of litters with resorptions, dead fetuses, nonlive or affected implants, and anomalies--Chi Square Test for Independence for differences among treatment groups, Test for Linear Trend on Proportions, and Fisher's Exact Test for pairwise comparisons.

Compliance

- A signed Statement of No Data Confidentiality Claim, dated October 24, 1990, was provided.

- A signed Statement of Compliance with EPA GLPs; dated February 4 and 6, 1991, was provided.

- A signed Quality Assurance Statement, dated December 6, 1990, was provided.

C. RESULTS

Test Material Analysis

Purity of the test compound was determined by chromatography to be approximately 97%. Analyses conducted on dosing solutions on three occasions for concentration revealed a range of 89.8%-110% of nominal values. Homogeneity analyses, conducted on low and high dosing solutions, were within a range of 3%-4%. Stability of the dosing solutions for 7 days in refrigerated storage revealed values of 95.9%-104% of target; for 24 hours at ambient temperature, stability was 97.5% of target.

Maternal Toxicity

Mortality: Compound-related mortality was observed at the mid-dose (13%) and high-dose (25%) levels. During the dosing period, four does died at 7.0 mg/kg/day (one on GD 16 and three on GD 19). These does showed clinical signs including ataxia, salivation, prone positioning and tremors prior to death. Two does died at 2.5 mg/kg/day (one on GD 12 and one on GD 15); the cause of death could not be determined. Two does at 0.1 mg/kg/day were sacrificed because of premature deliveries (one on GD 23 and one on GD 30 before scheduled sacrifice).

Abortion: No abortions were noted.

Clinical observations: Compound-related clinical signs were observed at 7.0 mg/kg/day; all does at this dose level exhibited ataxia at some time during the dosing period. Other anticholinesterase-related activities also exhibited during the dosing period at the highest dose level included prone positioning, tremors, excitation, salivation, and difficulty in breathing. An additional incidental clinical sign noted at all dose levels was soft feces. Similar observations were noted in a range-finding study in rabbits (no. 60C-4629-30) and in a rat study (no. 60C-4629-10/20).

Body weight: Compound-related effects were observed at 7.0 mg/kg/day. A summary of maternal body weight gain data for selected intervals is presented in Table 1. Body weights were comparable for all dose groups (data not shown). During the dosing period (GDs 7-19), mean body weight gain at 2.5 and 7.0 mg/kg/day decreased by 67% and 58%, respectively. The corrected mean body weight gain decreased (54%) significantly at 7.0 mg/kg/day (Table 1).

Food consumption: A summary of food consumption (g/kg/day) data is presented in Table 2A. A compound-related decrease in food consumption (g/day or g/kg/day) was observed at 7.0 mg/kg/day. Significant ($p<0.05$) decreases (12%) were observed in food consumption during GDs 7-19. On the other hand, a significant increase (27%) in food consumption at 0.1 mg/kg/day during the postdosing period (GDs 19-30) was not considered to be compound related.

The food efficiency decreased in all dose groups during the treatment period (GDs 7-19) compared to control (Table 2B). However, this decrease was not dose-dependent and therefore, the effect on food consumption was not considered to be treatment-related.

Gross pathology observations: A significant decrease in absolute and relative liver weights at 7.0 mg/kg/day was attributed to decreases in body weight. No compound-related effects were noted in gravid uterine weights at any dose level.

Cesarean section observations: No compound-related effects were noted for any parameter at any dose level. A summary of cesarean section data is presented in Table 3. No individual maternal and litter data were available to confirm the number of corpora lutea/litter and pre-implantation loss.

Developmental Toxicity

No compound-related anomalies were noted at any dose level. A summary of incidences of malformations is presented in Table 4.

External examinations: One fetus at 2.5 mg/kg/day had multiple malformations of the head, including microcephaly, bilateral microphthalmia, arhinia, and a small palate (Table 4). Malformations observed in other groups were gastroschisis (one mid-dose fetus and one high-dose fetus) and agenesis of the head (one control fetus and one high-dose fetus). The only variation found was clubbed limb without bone changes (one control and one mid-dose fetus; data not shown).

Visceral examinations: The following incidental visceral malformations were observed (Table 4): agenesis of the cerebral lobes of the brain (one mid-dose fetus), abnormal papillary muscles of the right ventricle (observed in two control fetuses and one fetus in each of the three dose groups), interventricular septal defect (one high-dose fetus), common truncus (one high-dose fetus), hypoplastic left ventricle of heart (one high-dose fetus), and enlarged gall bladder (observed in 11 controls, 5 low-dose fetuses, one mid-dose fetus, and one high-dose fetuse). Variations were noted in all dose groups and included liver-like tissue on gall bladder, enlarged right ventricle of the brain, and abnormal number of papillary muscles of the right ventricle (data not shown).

Skeletal examinations: The following incidental skeletal malformations were observed (Table 4): fused sternebrae (one low-dose fetus), agenesis of rib (one mid-dose fetus), fused rib cartilage (two mid-dose fetuses), agenesis of vertebra (one control and one mid-dose fetus), and fused lumbar and thoracic centra (one mid-dose fetus). Variations were noted in all dose groups and included ribs and ossification of thoracic arch (data not shown).

D. REVIEWERS' DISCUSSION/CONCLUSIONS

Acceptance Criteria

The reviewers have completed an Acceptance Criteria check list which is included as Attachment I. Criterion 2 (at least 12 does/group) was not fulfilled due to high mortality; criterion 12 (corpora lutea) was only partially fulfilled (individual data were not submitted). All other criteria were satisfied.

The study was conducted according to FIFRA Subdivision F Guidelines and was adequately reported. The investigators' conclusions were substantiated by the data presented.

Although survival of high dose pregnant does was reduced, and the number of litters available for examination was less than recommended in the guidelines, the data clearly show that dichlorvos was not a developmental toxicant- under the study conditions.

The data developed in the preliminary study reinforces the choice of the dose levels and the conclusions in the definitive study, since there was maternal mortality at 10 mg/kg/day, but none at 5 mg/kg/day or 2.5 mg/kg/day. Cholinesterase inhibition occurred at 2.5 (43.4% of control for RBC and 60.9% of control for plasma) and 10 mg/kg/day (14.5% of controls for RBC and 18.6% of controls for plasma). For this study, there was possible developmental toxicity demonstrated as reduced fetal body wieght at 10 mg/kg/day. None was seen at 5 mg/kg/day.

Based on these considerations and the data presented in the definitive study, maternal toxicity NOEL and LOEL were demonstrated at 0.1 mg/kg/day and 2.5 mg/kg/day, respectively.

The NOEL for developmental toxicity was 7 mg/kg/day, the high dose tested.

The study is classified Core Minimum.

TABLE 1. Mean Body Weight Gain (g ± S.E.M.)[a]

Dose Group (mg/kg/day)	Prior-to-Dosing Period (GD 0-7)[b,c]	Dosing Period (GD 7-19)[c]	Gestation Period (GD 0-30)[c]	Corrected Body Weight Change[c,d]
0	335 ± 234	138 ± 71	600 ± 61	140 ± 63.8
0.1	312 ± 95	138 ± 27	701 ± 35	335 ± 66.4
2.5	324 ± 109	45 ± 32	663 ± 44	203 ± 63.7
7.0	259 ± 78	58 ± 41	586 ± 49	64 ± 33.9*

[a]Data were extracted from study no. 60C-4629-30/40, Table 2.

[b]Calculated by the reviewers

[c]Includes all does pregnant at sacrifice; mean ± S.E.M.

[d]Weight gain during gestation minus gravid uterine weight

*Significantly different from control ($p<0.05$)

TABLE 2A. Mean Food Consumption (g/kg/day ± S.E.M.)[a]

Dose Group (g/kg/day)	Prior-to-Dosing Period (GD 0-7)	Dosing Period (GD 7-19)	Post-Dosing Period (GD 19-30)	Entire Gestation Period (GD 0-30)
0	53.9 ± 2.0	43.6 ± 1.1[b]	34.7 ± 2.0	42.1 ± 1.1
0.1	56.2 ± 1.6	46.8 ± 2.5	44.0 ± 1.9**	47.6 ± 1.9
2.5	54.9 ± 2.0	41.3 ± 3.3	38.7 ± 1.5	43.1 ± 2.4
7.0	51.0 ± 1.3	38.4 ± 2.3	38.3 ± 1.1	42.4 ± 1.1

[a]Data were extracted from study no. 60C-4629-30/40, Table 4.

[b]Significant trend ($p < 0.01$)

**Significantly different from control ($p<0.01$)

TABLE 2B. Mean Food Efficiency (% efficiency of food utilization)[a,b]

Dose Group (g/kg/day)	Prior-to-Dosing Period (GD 0-7)	Dosing Period (GD 7-19)	Entire Gestation Period (GD 0-30)
0	624.6 ± 488	285.0 ± 609	1349.9 ± 509
0.1	550.9 ± 168	276.4 ± 220	1418.7 ± 155
2.5	579.7 ± 159	-1.1 ± 195	1558.0 ± 356
7.0	504.2 ± 139	57.4 ± 576	1372.3 ± 348

[a]Data extracted from study no. 60C-4629-30/40, Tables II-1, and II-5.

[b]Calculated by the reviewer; $\frac{\text{grams body weight change per unit time}}{\text{grams food consumption per unit time}} \times 100$

TABLE 3. Cesarean Section Observations[a]

Parameter	Dose Level (mg/kg/day) 0	0.1	2.5	7.0
No. animals assigned	16	16	16	16
No. animals pregnant	14	14	13	13
Pregnancy rate (%)	88	88	82	82
Maternal wastage				
No. died/nonpregnant	0	0	0	0
No. died/pregnant	0	0	2	4
No. nonpregnant	2	2	3	3
No. aborted	0	0	0	0
No. premature delivery	0	2	0	0
No. does with live fetuses	14	12	11	9
Total corpora lutea	-[b]	-	-	-
Corpora lutea/doe	10.4 ± 0.6	10.8 ± 0.6	10.0 ± 0.7	10.1 ± 0.6
Total implantations[d]	98	69	89	97
Implantations/doe	7.0 ± 0.8	4.9 ± 0.8	6.8 ± 1.1	7.4 ± 0.4
Total live fetuses[d]	91	57	69	66
Live fetuses/doe	6.5 ± 0.8	4.8 ± 0.8	6.3 ± 1.0	7.3 ± 0.4
Total resorptions	5	2	6	1
Early	4	2	3	1
Middle	1	0	1	0
Late	0	0	2	0
Resorptions/doe	0.4 ± 0.2	0.2 ± 0.1	0.6 ± 0.3	0.1 ± 0.1
Total dead fetuses	2	0	0	0
Dead fetuses/doe	0.1 ± 0.1	0	0	0
Fetal weight/litter (g)	50.6 ± 2.4	56.7 ± 2.3	53.2 ± 2.5	50.3 ± 1.4
Preimplantation loss (%)	33	53	35	25
Postimplantation loss (%)[d]	6	4	6	2
Sex ratio (% male)	43	56	56	58

[a]Data were extracted from study no. 60C-4629-10/20, Table 5 and Appendix II.

[b]Individual animal data not reported; therefore total no. cannot be calculated.

[c]Mean ± S.E.M.

[d]Calculated by the reviewers

TABLE 4. Incidences of Fetal Malformations[a]

Findings[b]	Dose Level (mg/kg/day) 0	0.1	2.5	7.0
No. fetuses (litters) examined	91 (14)	57 (12)	69 (11)	66 (9)
External malformations				
Agenesis of head	1	0	0	1
Arhinia	0	0	1	0
Microcephaly	0	0	1	0
Microphthalmia	0	0	1	0
Gastroschisis	0	0	1	1
Small palate	0	0	1	0
Small tongue	0	0	1	0
Astomia	0	0	1	0
Short tail	0	0	1	0
Total no. fetuses (litters) with external malformations	1	0	2 (2)	1
Total % fetuses (litters) with external malformations	1 (7)	0	3 (18)	2 (11)
Visceral malformations				
Agenesis of cerebral lobes	0	0	1	0
Abnormal papillary muscle				
bifurcated, right ventricle	2	1	1	1
trifurcated, left ventricle	1	0	0	0
enlarged, left ventricle	0	0	1	0
Interventricular septal defect	0	0	0	1
Enlarged gall bladder	11	5	1	1
Hypoplasic left ventricle of heart	0	0	0	1
Common truncus	0	0	0	1
Round heart	0	0	1	0
Enlarged bile duct	0	0	0	1
Total no. fetuses (litters) with visceral malformations	14 (6)	6 (3)	4 (3)	3 (3)
Total % fetuses (litters) with visceral malformations	15 (43)	11 (25)	6 (27)	5 (33)
Skeletal malformations				
Fused sternebrae	0	1	0	0
Fused ribs	0	0	1	0
Agenesis of the rib	0	0	1	0
Fused rib cartilage	0	0	2	0
Agenesis of the vertebra,				
caudal	0	0	1	0
cervical	1	0	0	0
lumbar	0	0	1	0
sacral	0	0	1	0
thoracic	0	0	1	0
Fused centra, lumbar	0	0	1	0
thoracic	0	0	1	0
Misaligned arch, lumbar	0	0	1	0
Misaligned centrum, lumbar	0	0	1	0
Branched rib	0	0	1	0
Total no. fetuses (litters) with skeletal malformations	1	1	4 (2)	0
Total % fetuses (litters) with skeletal malformations	1 (7)	2 (8)	6 (18)	0

[a]Data were extracted from study no. 60C-4629-30/40, Tables 6 and 7.

[b]More than one type of anomaly may be found in one fetus.

[c]Calculated by the reviewer

ATTACHMENT I

009840

83-3 Teratology Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1.	YES	Technical form of the active ingredient tested.
2.	NO	At least 20 pregnant animals/dose group for mice, rats, or hamsters are available. At least 12 pregnant animals/dose group for rabbits are available (three test groups and control group).
3.	YES	At the high dose, overt maternal effects such as slight weight loss are reported (or a limit dose is given, 1,000 mg/kg).
4.*	YES	At the low dose, no developmental toxicity is reported.
5.	YES	Dosing duration is at least during the period of major organogenesis, but may extend up to one day prior to term.
6.*	YES	Analysis for test material stability, homogeneity, and concentration in dosing medium.
7.	YES	Individual daily observations.
8.	YES	Individual body weights.
9.	YES	Individual food consumption.
10.	YES	Necropsy on all animals.
11.	YES	Individual uterine examination, including numbers of fetal deaths, early and late resorptions, and viable fetuses per sex.
12.	Y/N	All ovaries examined to determine number of corpora lutea.
13.	YES	Individual litter weights and/or individual fetal weights/sex/litter.
14.	YES	Individual fetal external examination.
15.	YES	Individual fetal skeletal examination for 1/3 to 1/2 of each litter for rodents and all for rabbits.
16.	YES	Individual fetal soft tissue examination.

Criteria marked with a * are supplemental, may not be required for every study.